Health effects associated with controlled exposures to cyanobacterial toxins

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The cyanobacterial toxins of concern as potential hazards to human health are those known to occur in widely in drinking water sources, and therefore may be present in water for human use. The toxins include a diverse range of chemical compounds, with equally diverse toxic effects.

Microcystins

The acute effects of microcystins have mainly been investigated by intraperitoneal (i.p.) dosing or oral dosing of experimental animals. It is well established that the main target in mammals for toxic effects is the liver, with adverse effects also seen in the small intestine. The initial rapid response of hepatocytes and enterocytes to microcystin exposure is cell deformation, caused by disruption of the cytoskeleton. *In vivo* this results in disintegration of the hepatic cellular architecture, with extensive bleeding into the liver resulting in rapid death of the animal. The i.p. LD_{50} over 24h for rodents for most microcystin variants is 50-100μg/kg bodyweight, and the concentration *in vitro* of microcystin causing 50% rat hepatocyte deformity in 30min is 30nm. Oral toxicity is 5-10 fold lower than i.p., and in mice is affected by age. In sheep acute lethal effects are seen from 18h after intra-ruminal dosing, with major liver damage.

Oral sub-chronic dosing trials with microcystin have been undertaken in mice and pigs, with the aim of determining a maximum No Observed Adverse Effect Level (NOAEL). In mice this was 40μg/kg/day and in pigs 100μg/kg/day (Lowest Observed Adverse Effect Level, LOAEL). Chronic toxicity trials in mice showed increased general mortality from infections, and evidence of increased tumours. Laboratory investigation of tumour promotion by microcystin has given strong evidence of non-phorbol ester type promotion, but not of genotoxicity. There is also evidence of liver carcinogenesis by very high repeated doses of microcystin in mice. There are no non-rodent long term studies of chronic or reproductive toxicity or carcinogenicity at present.

Cylindrospermopsins

These alkaloids have been investigated by i.p. and oral dosing of mice, but not yet of larger mammals. They are general cytotoxins, causing damage to liver, kidneys, gastrointestinal tract, endocrine organs, the immune system, vascular system and muscle. There appear to be two toxic responses, one rapid and possibly linked to a toxic metabolite formed by oxidation in the liver, and the other, a slower response due to protein synthesis inhibition. As a result i.p. LD_{50} at 24h was 2,100 mg/kg bodyweight and LD_{50} at 5-6days was 200μg/kg. Acute oral LD_{50} is not yet clearly established in experimental animals, but appears to be about 5,000μg/kg. Sub-chronic oral toxicity trials with purified toxin determined a NOAEL in male mice of 30μg/kg/day, based on kidney function. In-vitro and in-vivo genotoxicity and carcinogenicity testing of cylindrospermopsin have indicated that it is genotoxic and may be carcinogenic. Data is lacking for the detailed mechanism of action, reproductive toxicity, teratogenicity and chronic toxicity for both rodents and non-rodent species.

Anatoxins

Anatoxin-a and homo-anatoxin-a are small alkaloids, which act as an agonists at the neuromuscular junction, causing spontaneous firing and eventually death by respiratory failure. The acute i.p. LD_{50} is 375μg/kg in mice, the i.v. LD_{50} less than 100μg/kg, with intranasal LD_{50} 2000μg/kg and no lethality at 5000μg/kg oral dose. Repeated i.p. injection did not elicit resistance to toxicity. Data are available for sub-chronic oral toxicity. Anatoxin-a by gavage at 15,000μg/kg killed mice within 3 minutes, however 3 of 4 mice receiving 7,500μg/kg/day for 4 weeks survived with no post-mortem pathological changes. Nineteen of 20 mice receiving 3,000μg/kg/day for 4 weeks showed no effects. There is no evidence for reproductive, teratogenic or carcinogenic effects of anatoxin-a. Anatoxin-a(s) is an organophosphate anticholinesterase. The i.p. LD_{50} is 20μg/kg in mice, there are no oral toxicity data.

Saxitoxins

These alkaloids block sodium channels in nerve axons, causing loss of sensation and paralysis and are highly toxic. i.p. LD_{50} in mice is 8-10μg/kg, i.v. LD_{50} 3.4μg/kg and oral LD_{50} 260μg/kg for saxitoxin. Other saxitoxin variants have lower toxicity. Young rats are more susceptible than adults, and prior exposure appears to reduce susceptibility. There are no data for subchronic exposure, reproductive, teratogenic or carcinogenic effects of saxitoxins .